M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PID#: D030616

DATE: January 7, 2005

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SUBJECT: ODS POSTMARKETING SAFETY REVIEW
Consult: One-Year Post-Pediatric Exclusivity,
Postmarketing Adverse Event Review
Drug: Glucovance® (glyburide/metformin)
NDA #: 021-178
Pediatric Exclusivity Date: October 8, 2003

Executive Summary

As requested by the Office of Counter-Terrorism and Pediatric Development, this consult reviews the pediatric adverse events associated with Glucovance® (glyburide/metformin) during a 12-month period beginning October 8, 2003 (pediatric exclusivity approval date) through October 8, 2004. The data termination date that was used to allow for a one-month lag time for report entry was November 8, 2004.

To identify the adverse events, two AERS searches were conducted in the adult and pediatric age groups for the following time periods: 1) approval date (July 31, 2000) to October 8, 2004, and 2) October 8, 2003 through October 8, 2004.

Our AERS searches yielded no pediatric reports for the 12-month time period after pediatric exclusivity was granted. Because no pediatric reports were identified, we will continue to monitor adverse events for a second year for possibly a more meaningful analysis.

AERS Search Results

AERS searches including all sources - U.S. and foreign.

AERS search dates include two time periods: a) approval date (July 31, 2000) to October 8, 2004, and b) October 8, 2003 through October 8, 2004.

A. Adverse events from marketing Approval Date (July 31, 2000) to October 8, 2004:

1. Raw Counts of AERS Reports: see Table 1

Table 1: Raw Counts of AERS Reports †

	All reports (US)	Serious (US)	Death (US)
All ages ‡	480 (476)	35 (31)	4 (4)
Adults (≥17) [2]	435 (431)	31 (27)	3 (3)
Pediatrics (0-16) [2]	0 (0)	0 (0)	0 (0)

† Counts may include duplicate reports
‡ Null ages included
[2] Null ages not included

2. Top 20 reported event preferred terms (shown by number of terms and percent of total reports) and labeling status of these events (Underlined denotes Unlabeled):

All Ages:
diarrhea (98; 20.4%), blood glucose increased (86; 17.92%), nausea (44; 9.17%), blood glucose decreased (38; 7.92%), dizziness (37; 7.71%), hypoglycemia (33; 6.88%), asthenia (31; 6.46%), tremor (20; 4.17%), abdominal pain (18; 3.75%), headache (17; 3.54%); diabetes mellitus inadequate control (16; 3.33%), fatigue (16; 3.33), flatulence (16; 3.33%), vision blurred (15; 3.13%), weight decreased (15; 3.13%), dyspepsia (14; 2.92%), hyperhidrosis (13; 2.71%), weight increased (13; 2.71%), abdominal pain upper (12; 2.50%); blood glucose fluctuation (12; 2.50%)

Adults:
diarrhea (90; 20.69%), blood glucose increased (77; 17.70%), nausea (39; 8.97%), blood glucose decreased (35; 8.05%), dizziness (33; 7.59%), hypoglycemia (31; 7.13%), asthenia (29; 6.67%), tremor (20; 4.60%), fatigue (16; 3.68%), flatulence (16; 3.68%), abdominal pain (15; 3.45%), headache (15; 3.45%), weight decreased (15; 3.45%), diabetes mellitus inadequate control (14; 3.22%), vision blurred (14; 3.22%), dyspepsia (13; 2.99%), hyperhidrosis (13; 2.99%), weight increased (13; 2.99%), abdominal pain upper (11; 2.53%), blood glucose fluctuation (11; 2.53%)

Pediatrics:
None.

B. Adverse events from Pediatric Exclusivity approval date (October 8, 2003) through October 8, 2004:

1. Raw Counts of AERS Reports: see Table 2

Table 2: Raw Counts of AERS Reports †

	All reports (US)	Serious (US)	Death (US)
All ages ‡	171 (168)	13 (10)	0 (0)
Adults (≥17) [2]	161 (158)	11 (8)	0 (0)
Pediatrics (0-16) [2]	0 (0)	0 (0)	0 (0)

† Counts may include duplicate reports
‡ Null ages included
[2] Null ages not included

2. Top 20 reported event preferred terms (shown by number of terms and percent of total reports) and labeling status of these events (Underlined denotes Unlabeled):

All Ages:
diarrhea (30; 17.54%), blood glucose increased (29; 16.96%), hypoglycemia (20; 11.70%), nausea (18; 10.53%), dizziness (16; 9.36%), blood glucose decreased (10; 5.85%), constipation (9; 5.26%), asthenia (8; 4.68%), tremor (8; 4.68%), weight increased (8; 4.68%), fatigue (7; 4.09%), hyperhidrosis (7; 4.09%), blood glucose fluctuation (6; 3.51%), dyspepsia (6; 3.51%), stomach discomfort (6; 3.51%), abdominal pain upper (5; 2.92%), flatulence (5; 2.92%), headache (5; 2.92%), weight decreased (5; 2.92%), abdominal pain (4; 2.34%)

Adults:
diarrhea (30; 18.63%), blood glucose increased (27; 16.77%), hypoglycemia (19; 11.80%), nausea (17; 10.56%), dizziness (15; 9.32%), blood glucose decreased (10; 6.21%), constipation (9; 5.59%), asthenia (8; 4.97%), tremor (8; 4.97%), weight increased (8; 4.97%), fatigue (7; 4.35%), hyperhidrosis (7; 4.35%), blood glucose fluctuation (6; 3.73%), dyspepsia (6; 3.73%), abdominal pain upper (5; 3.11%), flatulence (5; 3.11%), stomach discomfort (5; 3.11%), weight decreased (5; 3.11%), feeling abnormal (4; 2.48%), feeling hot (4; 2.48%)

Pediatrics:
None.

Postmarketing Review of All Pediatric Adverse Event Reports from October 8, 2003 through October 8, 2004:

Not applicable as no pediatric reports were submitted during this time period.

Conclusion

Our AERS search yielded no pediatric reports for the 12-month time period after pediatric exclusivity was granted. We will continue to monitor adverse events for a second year for possibly a more meaningful analysis.

Limitations of the Adverse Event Reporting System (AERS)

The voluntary or spontaneous reporting of adverse events from health care professionals and consumers in the U.S reflects underreporting and also duplicate reporting. For any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s). The main utility of a spontaneous reporting system, such as AERS, is to provide signals of potential drug safety issues. Therefore, counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing drug risk between drugs.

January 7, 2005

Joslyn Swann, Pharm.D.
Safety Evaluator

Date Signed

Concur:

January 7, 2005

Lanh Green, Pharm.D., MPH
Team Leader

Date Signed

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